



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/SE98/00641 <b>(22) International Filing Date:</b> 7 April 1998 (07.04.98) <b>(30) Priority Data:</b> 9701304-9                      9 April 1997 (09.04.97)                      SE <b>(71) Applicant (for all designated States except US):</b> ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts WD4 8DH (GB). <b>(71) Applicant (for MG only):</b> ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> McINALLY, Thomas [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). TINKER, Alan [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> COMPOUNDS  <b>(57) Abstract</b> <p>There are provided novel compounds of formula (I) wherein A represents a five membered heterocyclic aromatic ring containing 1 to 3 heteroatoms which may be the same or different and are selected from O, N and S; or a six membered heterocyclic aromatic ring containing 1 to 3 nitrogen atoms; and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined in the Specification and pharmaceutically acceptable salts thereof and enantiomers and tautomers thereof; together with processes for their preparation, compositions containing them and their use in therapy. The compounds are inhibitors of nitric oxide synthase and are thereby particularly useful in the treatment or prophylaxis of inflammatory disease and pain.</p> <div style="text-align: center;"> <p>(I)</p> </div>		

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## COMPOUNDS

Field of the Invention

The present invention relates to novel compounds which are aminopyrimidine derivatives.

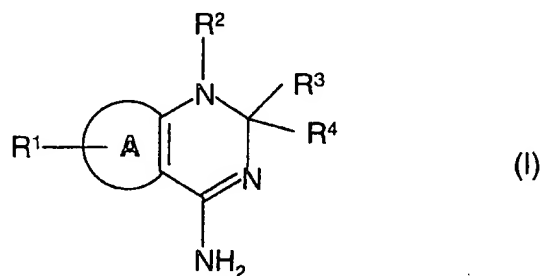
- 5 The invention also concerns related aspects including processes for the preparation of the compounds, compositions containing them and their use as pharmaceuticals. There are also provided chemical intermediates useful for the production of the compounds.

Background of the Invention

- 10 Nitric oxide is produced in mammalian cells from L-arginine by the action of specific nitric oxide synthases (NOSs). These enzymes fall into two distinct classes - constitutive NOS (cNOS) and inducible NOS (iNOS). At the present time, two constitutive NOSs and one inducible NOS have been identified. Of the constitutive NOSs, an endothelial enzyme (ecNOS) is involved with smooth muscle relaxation and the regulation of blood pressure
- 15 and blood flow, whereas the neuronal enzyme (ncNOS) serves as a neurotransmitter and appears to be involved in the regulation of various biological functions such as cerebral ischaemia. Inducible NOS has been particularly implicated in the pathogenesis of inflammatory diseases. Regulation of these enzymes should therefore offer considerable potential in the treatment of a wide variety of disease states (J. E. Macdonald, Ann. Rep. Med. Chem., 1996, 31, 221 - 230).
- 20

Disclosure of the Invention

According to the invention, there is provided a compound of formula (I):



25

wherein:-

R<sup>1</sup> represents hydrogen, alkyl C1 to 6, alkoxy C1 to 6, halogen or trifluoromethyl;

R<sup>2</sup> represents hydrogen or alkyl C1 to 6;

A represents a five membered heterocyclic aromatic ring containing 1 to 3 heteroatoms which may be the same or different and are selected from O, N and S; or a six membered

5 heterocyclic aromatic ring containing 1 to 3 nitrogen atoms;

(i) R<sup>3</sup> represents phenyl, a six membered heterocyclic aromatic ring containing 1 to 3 nitrogen atoms, or a five membered heterocyclic aromatic ring containing 1 to 3 heteroatoms which may be the same or different and are selected from O, N and S, which phenyl or heterocyclic aromatic ring may be optionally substituted by alkyl C1 to 6, alkenyl C2 to 6,  
10 alkynyl C2 to 6, alkoxy C1 to 6, halogen, hydroxy, alkylthio C1 to 6, cyano, trifluoromethyl, nitro or a group -NR<sup>5</sup>R<sup>6</sup>;

and R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> independently represent hydrogen or alkyl C1 to 6;

or

(ii) R<sup>3</sup> represents alkyl C1 to 8, alkenyl C2 to 8 or alkynyl C2 to 8;

15 and R<sup>4</sup> represents hydrogen or alkyl C1 to 6;

or

(iii) R<sup>3</sup> and R<sup>4</sup> together represent (CH<sub>2</sub>)<sub>a</sub> · Z · (CH<sub>2</sub>)<sub>b</sub>, Z representing N(COOR<sup>7</sup>),

wherein R<sup>7</sup> represents alkyl C1 to 6 or haloalkyl C1 to 6, or R<sup>7</sup> represents a group

(CH<sub>2</sub>)<sub>n</sub>YR<sup>9</sup> wherein n represents an integer from 2 to 5, Y represents O, S or a bond and

20 R<sup>9</sup> represents alkyl C1 to 6 optionally substituted by halogen or nitro, or R<sup>9</sup> represents

phenyl optionally substituted by alkyl C1 to 6, halogen or nitro; and

a and b independently represent an integer 1 to 3, provided that a + b is 3 or 4;

or

(iv) R<sup>3</sup> and R<sup>4</sup> together represent (CH<sub>2</sub>)<sub>a</sub> · Z · (CH<sub>2</sub>)<sub>b</sub>, Z representing N(COR<sup>8</sup>),

25 wherein R<sup>8</sup> represents phenyl, a six membered heterocyclic aromatic ring containing 1 to 3 nitrogen atoms or a five membered heterocyclic aromatic ring containing 1 to 3

heteroatoms which may be the same or different and are selected from O, N and S, which

phenyl or heterocyclic aromatic ring may be optionally substituted by alkyl C1 to 6, alkoxy

C1 to 6, halogen, nitro, cyano, trifluoromethyl, alkylsulphonyl C1 to 6 or aminosulphonyl;  
and

a and b independently represent an integer 1 to 3, provided that  $a + b$  is 3 or 4;  
or pharmaceutically acceptable salts, enantiomers, racemates and tautomers thereof.

5

The invention further provides a process for the preparation of such compounds or a  
pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

According to the invention there is also provided a compound of formula (I), or a  
10 pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, for use as a  
medicament.

Another aspect of the invention provides the use of a compound of formula (I) or a  
pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, in the  
15 manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in  
which inhibition of nitric oxide synthase activity is beneficial.

A more particular aspect of the invention provides the use of a compound of formula (I) or  
a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, in the  
20 manufacture of a medicament, for the treatment or prophylaxis of inflammatory disease.

According to the invention, there is also provided a method of treating, or reducing the risk  
of, diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial  
which comprises administering to a person suffering from or at risk of, said disease or  
25 condition, a therapeutically effective amount of a compound of formula (I) or a  
pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

More particularly, there is also provided a method of treating, or reducing the risk of,  
inflammatory disease in a person suffering from or at risk of, said disease, wherein the  
30 method comprises administering to the person a therapeutically effective amount of a

compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

The compounds of the present invention may also be used advantageously in combination  
5 with a second pharmaceutically active substance, particularly in combination with a  
selective inhibitor of the inducible isoform of cyclooxygenase (COX-2). Thus, in a further  
aspect of the invention there is provided the use of a compound of formula (I) or a  
pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, in combination  
10 with a COX-2 inhibitor for the treatment of inflammation, inflammatory disease and  
inflammatory related disorders. And there is also provided a method of treating, or  
reducing the risk of, inflammation, inflammatory disease and inflammatory related  
disorders in a person suffering from or at risk of, said disease or condition, wherein the  
method comprises administering to the person a therapeutically effective amount of a  
15 compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or  
tautomer thereof in combination with a COX-2 inhibitor.

Preferably, A represents a thieno ring. Especially preferred embodiments are where the  
compound of formula (I) is a thieno[2,3-*d*]pyrimidine or a thieno[3,2-*d*]pyrimidine.

20 In another preferred embodiment, A represents a pyrido ring. Especially preferred  
embodiments are where the compound of formula (I) is a pyrido[2,3-*d*]pyrimidine,  
pyrido[3,2-*d*]pyrimidine, pyrido[3,4-*d*]pyrimidine or pyrido[4,3-*d*]pyrimidine.  
Pyrido[3,2-*d*]pyrimidine compounds of formula (I) are the most preferred.

25 Preferably, R<sup>3</sup> represents phenyl, cyclopropyl, ethyl, thiazolyl, ethynyl or furanyl.

In another preferred embodiment, wherein R<sup>3</sup> and R<sup>4</sup> are in accordance with option (iii) in  
formula (I), Z represents N(COOC<sub>2</sub>H<sub>5</sub>), and a and b each has a value of 2.

30 Especially preferred compounds of the invention include:

- 7-amino-4,5-dihydro-5-phenylthieno[3,2-*d*]pyrimidine;  
5-cyclopropyl-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine;  
5-ethyl-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine;  
5-(2-thiazolyl)-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine;  
5 5-(2-furyl)-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine;  
7-amino-4,5-dihydro-5-ethynylthieno[3,2-*d*]pyrimidine;  
ethyl 7'-aminospiro[piperidine-4,5'-(4'*H*)-thieno[3,2-*d*]pyrimidine]-1-carboxylate;  
ethyl 4'-amino-3'-chlorospiro[piperidine-4,6'-(7'*H*)-thieno[2,3-*d*]pyrimidine]-1-carboxylate;  
4'-amino-(4-cyanobenzoyl)-spiro[piperidine-4,2'-(1'*H*)-(pyrido[3,2-*d*]pyrimidine)];  
10 4'-amino-(2-thienoyl)-spiro[piperidine-4,2'-(1'*H*)-(pyrido[3,2-*d*]pyrimidine)];  
ethyl 4'-aminospiro[piperidine-4,2'-(1'*H*)-(pyrido[3,2-*d*]pyrimidine)]-1-carboxylate;  
4'-amino-(4-cyanobenzoyl)-spiro[piperidine-4,2'-(1'*H*)-(pyrido[3,4-*d*]pyrimidine)];  
ethyl 4'-aminospiro[piperidine-4,2'-(1'*H*)-(pyrido[3,4-*d*]pyrimidine)]-1-carboxylate;  
4'-amino-(4-cyanobenzoyl)-spiro[piperidine-4,2'-(1'*H*)-(pyrido[4,3-*d*]pyrimidine)];  
15 ethyl 4'-aminospiro[piperidine-4,2'-(1'*H*)-(pyrido[2,3-*d*]pyrimidine)]-1-carboxylate;  
4-amino-2-(2-thienyl)-pyrido[3,2-*d*]pyrimidine;  
7'-amino-1-(6-cyano-3-pyridinecarbonyl)spiro[piperidine-4,5'-(4'*H*)-(thieno[3,2-*d*]-  
pyrimidine)];  
and pharmaceutically acceptable salts, enantiomers or tautomers thereof.

20

Unless otherwise indicated, the term "C1 to 6 alkyl " referred to herein denotes a straight or branched chain alkyl group having from 1 to 6 carbon atoms or a cyclic alkyl group having from 3 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, cyclopentyl and cyclohexyl.

25

Unless otherwise indicated, the term "C2 to 6 alkenyl " referred to herein denotes a straight or branched chain alkyl group having from 2 to 6 carbon atoms and including one double bond or a cyclic alkyl group having from 3 to 6 carbon atoms and including one double bond. Examples of such groups include ethenyl, 1- and 2-propenyl, 2-methyl-2-propenyl,  
30 2-butenyl, cyclopentenyl and cyclohexenyl.

Unless otherwise indicated, the term "C2 to 6 alkynyl" referred to herein denotes a straight or branched chain alkyl group having from 2 to 6 carbon atoms and including one triple bond. Examples of such groups include ethynyl, 1- and 2-propynyl and 2-butynyl.

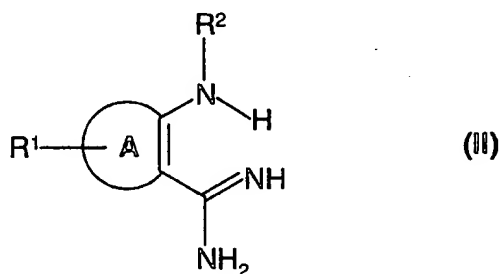
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Unless otherwise indicated, the term "C1 to 6 alkoxy" referred to herein denotes a straight or branched chain alkoxy group having from 1 to 6 carbon atoms. Examples of such groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy and t-butoxy.

10 Other groups, for example, alkylthio, haloalkyl, alkylsulphonyl, are to be interpreted similarly.

The process mentioned above, for the preparation of compounds of the invention, or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof comprises:

15 (a) reaction of a compound of formula (II)



wherein A, R<sup>1</sup> and R<sup>2</sup> are as defined above,

with a compound of formula (III) or an acetal derivative thereof

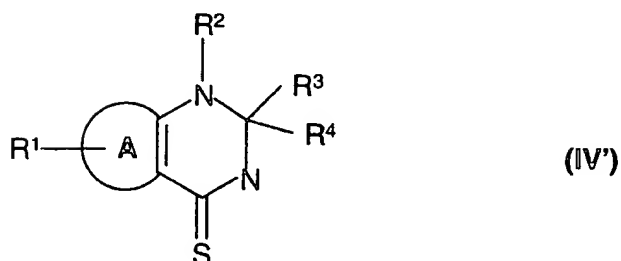
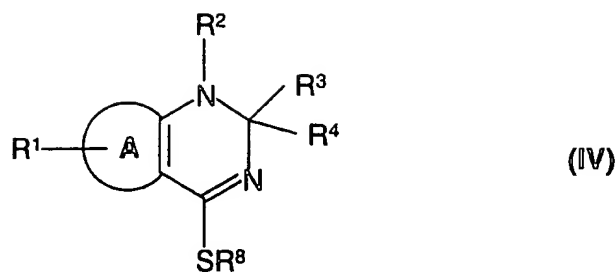
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wherein R<sup>3</sup> and R<sup>4</sup> are as defined above; or

(b) reaction of a compound of formula (IV) or (IV')





wherein A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined above, and R<sup>8</sup> represents an alkyl group;

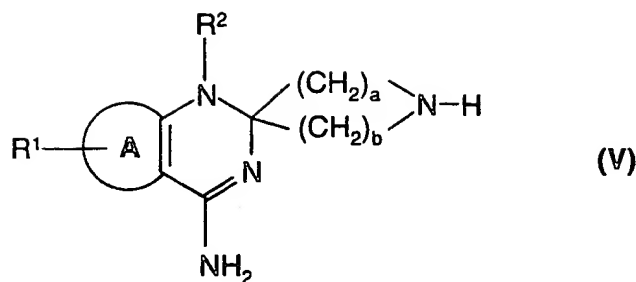
5 with ammonia or an equivalent thereof; or

(c) preparation of a compound of formula (I) in which R<sup>3</sup> and R<sup>4</sup> are according to option (i) in the general definition of formula (I) given above and one or both of R<sup>5</sup> and R<sup>6</sup> represents alkyl C1 to 6, by alkylation of a corresponding compound in which one or both of R<sup>5</sup> or R<sup>6</sup> represents hydrogen; or

10 (d) preparation of a compound of formula (I) in which R<sup>2</sup> represents alkyl C1 to 6, by alkylation of a corresponding compound in which R<sup>2</sup> represents hydrogen; or

(e) deprotection of a compound of formula (I) in which one or more nitrogen atoms and/or another atom is protected; or

(f) preparation of a compound of formula (I) in which R<sup>3</sup> and R<sup>4</sup> are in accordance with  
 15 option (iv) in the general definition of formula (I) given above, by reacting a compound of formula (V)



wherein A, R<sup>1</sup>, R<sup>2</sup>, a and b are as defined above,

with a compound of formula (VI)



wherein X represents COOR<sup>7</sup> or COR<sup>8</sup>, R<sup>7</sup> and R<sup>8</sup> being as above, and L is a leaving group;

and where desired or necessary converting the resultant compound of formula (I), or  
 10 another salt thereof, into a pharmaceutically acceptable salt thereof, or vice versa, and  
 where desired converting the resultant compound of formula (I) into an optical isomer thereof.

In process (a), the reaction of compounds of formulae (II) and (III) may be performed by  
 15 stirring the reactants in an inert solvent at a temperature between room temperature and the  
 boiling temperature of the solvent for a period of up to 72 hours, or until reaction is complete.  
 We have found that it is often convenient to use the compounds of formula (III) in a protected  
 form, for example as an acetal such as the diethoxy acetal. The process is then preferably  
 carried out in the presence of an acid catalyst. The required acetals may be formed by reacting  
 20 an unprotected compound of formula (III) with an alcohol such as ethanol using methods that  
 are well known in the art.

In process (b), the reaction may be performed by bubbling ammonia gas through a solution of  
 the compound of formula (IV) or (IV') in an inert polar solvent. Alternatively, the reaction  
 25 may be performed by treating a solution of the compound of formula (IV) or (IV') in a polar

protic solvent with aqueous ammonia, ammonia in acetonitrile or with methanolic ammonia or by treating the compound of formula (IV) or (IV') with ammonium iodide and ammonia in alcohol solution.

- 5 In processes (c) and (d), the alkylation reaction may be performed by processes well known in the art. For example, the amine may be reacted with an alkyl halide, especially an alkyl bromide or iodide.

10 In process (e), protecting groups for amines include alkyl, aralkyl, acyl, acyl sulphonyl, aryl sulphonyl and trialkylsilyl. Terminal alkynes may also be protected using a trialkylsilyl group. When the protecting group is trialkylsilyl, this group may be removed using, for example, tetra-n-butylammonium fluoride. Other protecting groups and further details of processes for their removal may be found by reference to the standard text "Protecting Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts.

15

In process (f), the reaction may be performed by combining the reactants in an inert solvent at a suitable temperature in the presence of a base, for example, pyridine. Although a number of standard leaving groups L are suitable, we prefer that L represents a halogen, especially chlorine or bromine.

20

The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids may be of utility in the preparation and  
25 purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, methanesulphonic and benzenesulphonic acids.

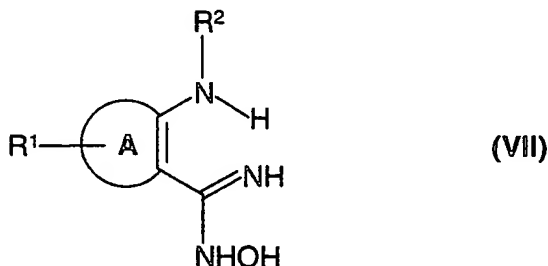
Salts of compounds of formula (I) may be formed by reacting the free base, or a salt,  
30 enantiomer or tautomer thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a

solvent in which the salt is soluble, for example water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed *in vacuo* or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin.

5

Novel intermediates of formulae (II), (IV), (IV') and (V) form another aspect of the invention.

Compounds of formula (II) may be prepared by reduction of a compound of formula (VII)

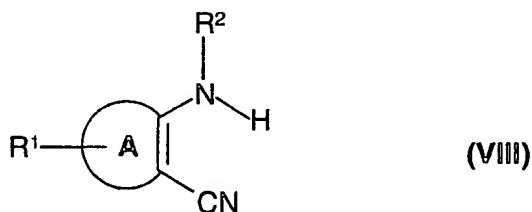


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wherein A, R<sup>1</sup> and R<sup>2</sup> are as defined above.

This reduction process may be performed by treating the compound of formula (VII) with  
15 hydrogen in the presence of palladium on carbon or rhodium on alumina or Raney nickel at elevated temperature and pressure, typically 65 °C and 30 atmospheres pressure.

Compounds of formula (VII) may be prepared by reaction of a compound of formula (VIII)



20

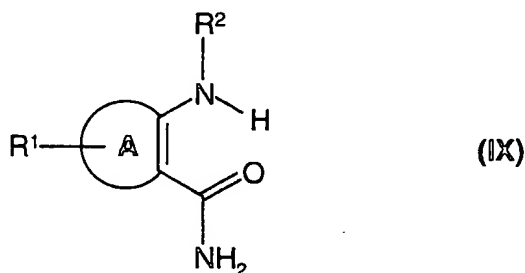
wherein A, R<sup>1</sup> and R<sup>2</sup> are as defined above,  
with hydroxylamine hydrochloride.

In this reaction, the two reactants may be heated together in the presence of a base, such as sodium methoxide, in methanol.

- 5 As alternative preparation methods for compounds of formula (II), a compound of formula (VIII) may be treated with a primary alcohol such as ethanol in the presence of acid, and subsequently treated with ammonium chloride to yield the compound of formula (II). Or a compound of formula (VIII) may be treated with a mixture of trimethylaluminium and ammonium chloride in a solvent such as toluene.

10

As a further alternative preparation method for compounds of formula (II), a compound of formula (IX)



wherein A, R<sup>1</sup> and R<sup>2</sup> are as defined above,

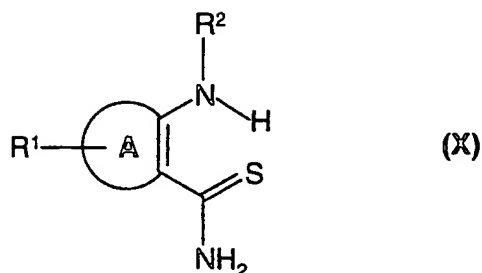
- 15 may be treated with ammonia.

The reaction will take place under standard conditions, although a preactivation step is normally necessary, for example using Meerwein's reagent.

- 20 Compounds of formula (III), (VIII) and (IX) are either known or may be made by conventional methods known *per se*.

- Compounds of formula (VIII) and (IX) in which R<sup>2</sup> represents alkyl C1 to 6 may be prepared by alkylation of a corresponding compound of formula (VIII) or (IX) in which R<sup>2</sup> represents  
25 hydrogen following process (d) above.

Compounds of formula (IV) may be prepared by reacting a compound of formula (X)



- 5 wherein A, R<sup>1</sup> and R<sup>2</sup> are as defined above,  
with a compound of formula (III) in the presence of an alkyl iodide.

The conditions for this reaction will be similar to those described above for process (a).

- 10 Compounds of formula (X) may be prepared by treating a compound of formula (IX) with  
Lawesson's reagent.

- Compounds of formula (II) may also be prepared by converting a compound of formula (X)  
into the corresponding alkylthio derivative by treatment with an alkyl halide (especially an  
15 alkyl iodide) and subsequently reacting with ammonia following a process analogous to that  
of process (b) above.

- Intermediate compounds may be used in protected form. Protecting groups and details of  
processes for their removal may be found by reference to the standard text "Protecting Groups  
20 in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts.

The compounds of the invention and intermediates thereto may be isolated from their  
reaction mixtures and, if necessary further purified, by using standard techniques.

- 25 The compounds of formula (I) may exist in enantiomeric forms. Therefore, all enantiomers,  
diastereomers, racemates and mixtures thereof are included within the scope of the invention.

The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example fractional crystallisation or HPLC.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified  
5 enantiomers, diastereomers, racemates or mixtures thereof.

The compounds of formula (I) may exist in alternative tautomeric forms. Compounds of formula (I) are provided in another tautomeric form or as a mixture thereof.

10 The compounds of formula (I), and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers, are useful because they possess pharmacological activity in animals. In particular, the compounds are active as inhibitors of the enzyme nitric oxide synthase. More particularly, they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase present in macrophages and as such are predicted to be useful in therapy, for  
15 example, as anti-inflammatory agents.

The compounds and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers are indicated for use in the treatment or prophylaxis of diseases or conditions in which synthesis or oversynthesis of nitric oxide synthase forms a contributory part. In  
20 particular, the compounds are indicated for use in the treatment of inflammatory conditions in mammals, including man.

Conditions that may be specifically mentioned are:

25 osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis and other arthritic conditions, inflamed joints;

eczema, psoriasis, dermatitis or other inflammatory skin conditions such as sunburn;

30 inflammatory eye conditions including uveitis and conjunctivitis;

lung disorders in which inflammation is involved, for example, asthma, bronchitis, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome;

bacteraemia, endotoxaemia (septic shock), aphthous ulcers, gingivitis, pyresis, pain and  
5 pancreatitis;

conditions of the gastrointestinal tract including Crohn's disease, atrophic gastritis, gastritis  
varialoforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, irritable  
bowel syndrome, damage to the gastrointestinal tract resulting from infections by, for  
10 example, *Helicobacter pylori*, or from treatments with non-steroidal anti-inflammatory drugs;

and other conditions associated with inflammation.

The compounds will also be useful in the treatment and alleviation of acute or persistent  
15 inflammatory or neuropathic pain or pain of a central origin.

The compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers,  
racemates and tautomers may also be useful in the treatment or prophylaxis of diseases or  
conditions in addition to those mentioned above. For example, the compounds may be useful  
20 in the treatment of atherosclerosis, cystic fibrosis, hypotension associated with septic and/or  
toxic shock, in the treatment of dysfunction of the immune system, as an adjuvant to short-  
term immunosuppression in organ transplant therapy, in the treatment of vascular  
complications associated with diabetes and in cotherapy with cytokines, for example TNF or  
interleukins.

The compounds of formula (I) may also show inhibitory activity against the neuronal isoform  
of nitric oxide synthase. Thus they may also be useful in the treatment of hypoxia, for  
example in cases of cardiac arrest and stroke, neurodegenerative disorders including nerve  
degeneration and/or nerve necrosis in disorders such as hypoxia, hypoglycaemia, epilepsy,  
30 and in external wounds (such as spinal cord and head injury), hyperbaric oxygen convulsions  
and toxicity, dementia, for example pre-senile dementia, Alzheimer's disease and AIDS-



related dementia, Sydenham's chorea, Parkinson's disease, Tourette's Syndrome, Huntington's disease, Amyotrophic Lateral Sclerosis, Korsakoff's disease, imbecility relating to a cerebral vessel disorder, sleeping disorders, schizophrenia, depression, autism, seasonal affective disorder, jet-lag, depression or other symptoms associated with Premenstrual Syndrome (PMS), anxiety and septic shock. Compounds of formula (I) may also be expected to show activity in the prevention and reversal of tolerance to opiates and diazepines, treatment of drug addiction, treatment of migraine and other vascular headaches, neurogenic inflammation, in the treatment of gastrointestinal motility disorders, cancer and in the induction of labour.

For the above mentioned therapeutic indications, the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of the solid form of between 1 mg and 2000 mg per day.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may be used on their own, or in the form of appropriate pharmaceutical compositions in which the compound or derivative is in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Administration may be by, but is not limited to, enteral (including oral, sublingual or rectal), intranasal, intravenous, topical or other parenteral routes.

Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988. The pharmaceutical composition preferably comprises less than 80% and more preferably less than 50% of a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may also be advantageously used in combination with a COX-2 inhibitor. Particularly preferred COX-2 inhibitors are Celecoxib and MK-966. The NOS inhibitor and the COX-2 inhibitor may either be formulated together within the same pharmaceutical composition for administration  
5 in a single dosage unit, or each component may be individually formulated such that separate dosages may be administered either simultaneously or sequentially.

The invention is illustrated, but in no way limited, by the following examples:

10

### Preparation 1

#### 2-Amidino-3-aminopyridine hydrochloride

##### (a) 3-Azido-2-cyanopyridine

A solution of 3-bromo-2-cyanopyridine (*Chem. Pharm. Bull.*, 1985, 33, 565) (2.6 g, 14.2  
15 mmol) and sodium azide (1.0 g, 15.3 mmol) in DMF (30 ml) was heated at 90 °C for 16 h. The resulting mixture was cooled, water was added and the whole was extracted with ethyl acetate. The combined extracts were washed with saturated brine and dried over magnesium sulphate. Evaporation of the solvent gave the product as an oil, which was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petrol  
20 (1:3 to 1:1) as eluent to afford the product. MS (EI)  $m/z$  145;  $^1\text{H}$  NMR ( $d_6$ -DMSO) 8.50 (1H, d), 8.09 (1H, d), 7.77 (1H, dd).

##### (b) 3-Amino-2-cyanopyridine

A solution of 3-azido-2-cyanopyridine (1.44 g, 9.9 mmol) in ethanol (100 ml) was hydrogenated over palladium on carbon (10%, 50 mg) at room temperature and 3.5 p.s.i for  
25 18 h. The catalyst was filtered off over Celite and the filtrate was concentrated to leave the product (1.16 g).  $^1\text{H}$  NMR ( $d_6$ -DMSO) 7.87 (1H, d), 7.33 (1H, dd), 7.22 (1H, d), 6.28 (2H, s).

##### (c) 3-Amino-2-(amino(hydroxyimino)methyl)pyridine

A suspension of 3-amino-2-cyanopyridine (1.18 g, 9.9 mmol), sodium methoxide (0.64 g,  
30 12 mmol) and hydroxylamine hydrochloride (0.83 g, 12 mmol) in ethanol (10 ml) was

heated under reflux for 1 h. The mixture was filtered and the filtrate concentrated to an oil, which was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (50:1 to 10:1) as eluent to afford the product as a yellow solid (0.82 g), MS (+CI)  $m/z$  153  $[M+H]^+$ ;  $^1H$  NMR ( $d_6$ -DMSO) 9.80 (1H, br. s), 7.80 (1H, dd), 7.10 (1H, d), 7.08 (1H, d), 6.62 (2H, s), 5.90 (1H, s).

(d) 2-Amidino-3-aminopyridine hydrochloride

A suspension of 3-amino-2-(amino(hydroxyimino)methyl)pyridine (0.82 g, 5.4 mmol) and wet Raney nickel (ca. 0.1 g) in ethanol (200 ml) was stirred under 3 atmospheres of hydrogen at 60 °C for 16 h. The catalyst was removed by filtration and the solvent evaporated to give the product as an oil, which was dissolved in a small amount of ethanol. Hydrogen chloride in ether (1N, 11 ml) was added with stirring and the precipitate was collected by filtration to give a solid. MS (+CI)  $m/z$  137  $[M+H]^+$ ,  $^1H$  NMR ( $d_6$ -DMSO) 9.15 (4H, br. s), 7.93 (1H, dd), 7.34 (1H, d), 7.26 (1H, d).

Preparation 2

4-Amidino-3-aminopyridine hydrochloride

(a) 3,5-Dichloro-4-formylpyridine

n-Butyllithium (1.6M in hexanes, 9.3 ml, 14.9 mmol) was added dropwise at 0 °C to a solution of diisopropylamine (1.95 ml, 14.9 mmol) in THF (30 ml). After 15 min. at 0 °C, the solution was cooled to -78 °C and 3,5-dichloropyridine (2.0 g, 13.5 mmol) was added. After 1 h, methyl formate (0.92 ml) was added and the mixture warmed to room temperature over 2 h, diluted with 1N hydrochloric acid and extracted twice with ethyl acetate. The extracts were washed with brine, dried over sodium sulphate and evaporated to give a yellow oil which solidified, m.p. 110-111 °C.

(b) 3,5-Chloro-4-cyanopyridine

A suspension of 3,5-dichloro-4-formylpyridine (1.0 g, 5.68 mmol) and hydroxylamine-O-sulphonic acid (0.96 g, 8.5 mmol) in water (20 ml) was heated at 70 °C for 16 h, then cooled and extracted twice with ethyl acetate. The extracts were washed with brine and dried over sodium sulphate. Evaporation of the solvent gave the product as an oil, which

was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (10:1) to afford the product. MS (+EI)  $m/z$  172/174/176;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 8.69 (2H, s).

(c) 5-Azido-3-chloro-4-cyanopyridine

- 5 This compound was prepared from 3,5-chloro-4-cyanopyridine following the method of Preparation 1(a) to give a solid. MS (+EI)  $m/z$  151 ( $\text{M}^+ - \text{N}_2$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 8.89 (1H, s), 8.69 (1H, s).

(d) 5-Amino-3-chloro-4-cyanopyridine

- 10 Tin (II) chloride (1.42 g, 7.5 mmol) was added to a solution of 5-azido-3-chloro-4-cyanopyridine (0.9 g, 5 mmol) in ethanol (20 ml) and water (0.3 ml). Bubbling ensued. The mixture was stirred for 1 h. and then extracted twice with ethyl acetate. The extracts were washed twice with saturated aqueous sodium bicarbonate and dried over sodium sulphate. Evaporation of the solvent gave the product as an oil, which was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (10:1) to afford the product. MS (+CI)  $m/z$  152 [ $\text{M} - \text{H}$ ] $^+$ ;  $^1\text{H}$  NMR ( $\text{d}_6\text{-DMSO}$ ) 8.15 (1H, s), 7.87 (1H, s), 6.88 (2H, s).

(e) 4-Amidino-3-aminopyridine hydrochloride

- This compound was prepared from 5-amino-3-chloro-4-cyanopyridine following the method of Preparation 1, steps (c) and (d) to give a solid. MS (+CI)  $m/z$  171 [ $\text{M} + \text{H}$ ] $^+$ ;  $^1\text{H}$  NMR ( $\text{d}_6\text{-DMSO}$ ) 9.54 (2H, s), 9.34 (2H, s), 8.27 (1H, s), 8.00 (2H, s), 7.55 (2H, d).

Preparation 3

3-Amidino-4-aminopyridine hydrochloride

- 25 (a) 4-Amino-3-cyanopyridine

This compound was prepared from 4-amino-3-formylpyridine following the method of Preparation 2(b) to give the product as a white solid. MS (+EI)  $m/z$  119 ( $\text{M}$ ) $^+$ ;  $^1\text{H}$  NMR ( $\text{d}_6\text{-DMSO}$ ) 8.38 (1H, s), 8.12 (1H, d), 7.02 (2H, s), 6.66 (1H, d).

(b) 3-Amidino-4-aminopyridine

To ammonium chloride (430 mg, 8.1 mmol) in toluene was added trimethylaluminium (2M in hexane, 4 ml, 8.1 mmol) at 5 °C and the mixture was stirred at room temperature for 2 h. 4-Amino-3-cyanopyridine (320 mg, 2.7 mmol) was added and the reaction mixture was heated at 80 °C overnight. The mixture was cooled, poured onto alumina in chloroform, quenched with ethanol and filtered. The filtrate was concentrated and triturated with ether  
5 to give a solid. MS (+EI)  $m/z$  119 (M-NH<sub>3</sub>)<sup>+</sup>.

### Example 1

#### 10 7-Amino-4,5-dihydro-5-phenylthienof[3,2-*d*]pyrimidine hydrochloride

##### (a) 3-Aminothiophene-2-thiocarboxamide

A solution of 3-aminothiophene-2-carboxamide (4.5 g, 31 mmol) in tetrahydrofuran was treated with Lawesson's Reagent (7.7 g, 190 mmol) and the solution was stirred at room temperature for 18 h. The solvent was removed and the residue purified by chromatography  
15 on silica gel using dichloromethane as eluent. The product was obtained as a yellow powder (2.8 g, 56%), m.p. 98-99 °C.

##### (b) 4,5-Dihydro-7-(methylthio)-5-phenylthienof[3,2-*d*]pyrimidine hydroiodide

A solution of 3-aminothiophene-2-thiocarboxamide (1.0 g, 6.3 mmol), methyl iodide (0.39 ml, 6.3 mmol) and benzaldehyde (0.67 g, 6.3 mmol) in acetonitrile was stirred at room  
20 temperature for 18 h. The product was collected by filtration, washed with acetonitrile, then ether and dried (1.58 g, 64%), m.p. 193-194 °C.

##### (c) 4,5-Dihydro-7-amino-5-phenylthienof[3,2-*d*]pyrimidine hydrochloride

A solution of 4,5-dihydro-7-(methylthio)-5-phenylthienof[3,2-*d*]pyrimidine hydroiodide (0.5 g, 1.29 mmol) in acetonitrile was saturated with dry ammonia gas and then heated at reflux  
25 for 20 h. The solvent was removed and the residue triturated with an ether/ethanol mixture to give the hydroiodide salt (92 mg) as a hygroscopic powder, m.p. 179-181 °C. This material was converted into the hydrochloride salt (m.p. 229-231 °C) by neutralisation followed by treatment with excess hydrogen chloride in ether.

Example 2

Following a process analogous to that of Example 1, the following compounds were prepared:

- 5 (a) 5-Cyclopropyl-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine hydrochloride, m.p. 195-196 °C.
- (b) 5-Ethyl-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine hydroiodide, m.p. 177 °C.
- (c) 5-(2-Thiazolyl)-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine hydroiodide trihydrate, m.p. 194-195 °C.
- 10 (d) 5-(2-Furyl)-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine hydroiodide trihydrate, m.p. 239-240 °C.

Example 3

- 15 7-Amino-4,5-dihydro-5-ethynylthieno[3,2-*d*]pyrimidine hydrochloride

(a) Following a process analogous to that of Example 1, the following compound was prepared:

7-Amino-4,5-dihydro-5-(2-(trimethylsilyl)ethynyl)thieno[3,2-*d*]pyrimidine hydroiodide, MS  $m/z$  250  $[M+H]^+$ .

- 20 (b) 7-Amino-4,5-dihydro-5-ethynylthieno[3,2-*d*]pyrimidine hydrochloride

A solution of the product of step (a) (0.47 g, 1.9 mmol) in tetrahydrofuran was treated with tetrabutylammonium fluoride (1 M in THF, 2.27 ml, 2.27 mmol). The solution was stirred at room temperature for 18 h and the solvent was removed under reduced pressure. The residue was purified by chromatography on aluminium oxide (Brockman Grade 1, neutral) using  
25 dichloromethane/methanol mixtures and the crude product fraction was further purified by preparative reverse-phase hplc. The product fractions were concentrated and treated with excess hydrogen chloride in ether to precipitate the hydrochloride salt. After trituration with ether the title compound hydrochloride salt was obtained as a cream powder (14.2 mg), m.p. 194-196 °C.

Example 4Ethyl 7'-aminospiro[piperidine-4,5'-(4'H)-(thieno-[3,2-d]pyrimidine)]-1-carboxylate hydroiodide5 (a) Ethyl 7'-(methylthio)spiro[piperidine-4,5'-(4'H)-(thieno-[3,2-d]pyrimidine)]-1-carboxylate hydroiodide

A solution of 3-aminothiophene-2-thiocarboxamide (0.5 g, 3.16 mmol), methyl iodide (0.2 ml, 3.16 mmol) and N-carbethoxy-4-piperidone (0.47 ml, 3.16 mmol) in acetonitrile was stirred at room temperature for 18 h. The product was collected by filtration, washed with  
10 acetonitrile and dried to leave a bright yellow solid (0.88 g), MS (FAB)  $m/z$  326  $[M+H]^+$ .

(b) Ethyl 7'-aminospiro[piperidine-4,5'-(4'H)-(thieno-[3,2-d]pyrimidine)]-1-carboxylate hydroiodide

A mixture of the product of Example 4(a) (0.88 g, 1.94 mmol) and ammonium iodide (0.28 g, 1.94 mmol) in a minimum volume of acetonitrile was saturated with dry ammonia gas  
15 and then heated at reflux for 6h. The solvent was evaporated and the residue purified by chromatography on neutral alumina eluting with dichloromethane/methanol mixtures, to give, after trituration with ether, the product, as a lemon-coloured powder (0.15 g), m.p. 239 °C (softens at 143 °C).

20 Example 5Ethyl 4'-amino-3'-chlorospiro[piperidine-4,6'-(7'H)-thieno[2,3-d]pyrimidine]-1-carboxylate hydrochloride.(a) 3-Amidino-2-amino-4-chlorothiophene hydrochloride

25 Trimethylaluminium (2.0M in toluene, 8.33 mmol, 4.2 ml) was added dropwise to a stirred solution of ammonium chloride (446 mg, 8.33 mmol) in toluene (10 ml) at 5 °C. After 2 h at room temperature, 2-amino-4-chloro-3-cyanothiophene (440 mg, 2.78 mmol) was added portionwise over 10 min. and the solution heated to 80 °C for 2 h, cooled, poured onto silica (2 g), and the mixture treated with methanol (10 ml) with stirring. After 5 min. the  
30 mixture was filtered, the solid washed with methanol, and the filtrate evaporated to give the

crude product as a brown solid (640 mg), MS (+CI)  $m/z$  176  $[M+H]^+$ , 300 MHz  $^1H$  NMR ( $d_6$ -DMSO) 9.07 (1H, br.s), 8.95 (1H, br.s), 6.92 (1H, br.s), 6.57 (1H, s) (also signals for excess ammonium chloride).

(b) Ethyl 4'-amino-3'-chlorospiro[piperidine-4,6'-(7'H)-thienof[2,3-d]pyrimidine]-1-carboxylate hydrochloride.

3-Amidino-2-amino-4-chlorothiophene hydrochloride (130 mg) was heated with N-carboethoxy-4-piperidone (0.6 mmol, 0.1 ml) at 90 °C for 2 h, cooled and evaporated. The residue was purified by flash column chromatography on neutral alumina eluting with dichloromethane/methanol mixtures, and the product was treated with 1N hydrogen chloride in diethyl ether to afford a beige solid, MS (+CI)  $m/z$  329  $[M+H]^+$ ,  $^1H$  NMR ( $d_6$ -DMSO) 6.34 (1H, s), 4.10 (2H, q, J 7.2 Hz), 3.79-3.64 (4H, m), 2.09-1.99 (4H, m), 1.24 (3H, t, J 7.2 Hz).

Example 6

4'-Amino-(4-cyanobenzoyl)-spiro[piperidine-4,2'-[1'H]-(pyrido[3,2-d]pyrimidine)] hydrochloride

A solution of 2-amidino-3-aminopyridine hydrochloride (0.22 g, 1.05 mmol), 1-(4-cyanobenzoyl)-4-piperidone ethylene ketal (1.08 g, 3.98 mmol) in 1M hydrogen chloride in ether (3 ml) and ethanol (15 ml) was stirred at 70 °C for 18 h. The mixture was cooled, concentrated and purified by flash column chromatography on neutral alumina, eluting with dichloromethane/methanol (10:1 to 5:1) as eluent to afford the product as a yellow solid, m.p. 173-175 °C.

Example 7

4'-Amino-(2-thienoyl)-spiro[piperidine-4,2'-[1'H]-(pyrido[3,2-d]pyrimidine)] hydrochloride

This compound was prepared from 2-amidino-3-aminopyridine hydrochloride following the method of Example 6, to give a yellow solid, m.p. 144-145 °C.



Example 8Ethyl 4'-aminospiro[piperidine-4,2'-[1'H]-(pyrido-[3,2-d]-pyrimidine)]-1-carboxylate  
5 hydrochloride

This compound was prepared from 2-amidino-3-aminopyridine hydrochloride following the method of Example 6, to give a yellow solid, m.p. 135-136 °C.

Example 94'-Amino-(4-cyanobenzoyl)-spiro[piperidine-4,2'-[1'H]-(pyrido-[3,4-d]-pyrimidine)]  
10 hydrochloride

This compound was prepared from 4-amidino-3-aminopyridine hydrochloride following the method of Example 6 to give a yellow solid. MS (+CI)  $m/z$  347 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (d<sub>6</sub>-  
15 DMSO) 10.76 (1H, s), 9.66 (1H, s), 8.96 (1H, s), 8.42 (1H, s), 8.15 (1H, s), 8.06 (1H, d), 7.96 (2H, d), 7.81 (1H, d), 7.60 (2H, d), 3.75-3.95 (2H, m), 3.35-3.6 (2H, m), 1.8-2.2 (4H, m).

Example 10Ethyl 4'-aminospiro[piperidine-4,2'-[1'H]-(pyrido-[3,4-d]-pyrimidine)]-1-carboxylate  
20 hydrochloride

This compound was prepared from 4-amidino-3-aminopyridine hydrochloride following the method of Example 6, to give a yellow solid. MS (+CI)  $m/z$  290 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (d<sub>6</sub>-  
25 DMSO) 8.24 (1H, s), 7.95 (1H, d), 7.60 (1H, s), 7.50 (1H, s), 4.04 (2H, q), 3.4-3.6 (4H, m), 1.6-1.9 (4H, m), 1.19 (3H, t).

Example 114'-Amino-(4-cyanobenzoyl)-spiro[piperidine-4,2'-[1'H]-(pyrido-[4,3-d]-pyrimidine)]  
30

hydrochloride

A suspension of 3-amidino-4-aminopyridine (0.56 g), 1-(4-cyanobenzoyl)-4-piperidone ethylene ketal (1.08 g, 3.98 mmol) and potassium carbonate (0.5 g) in ethanol (20 ml) was stirred at 70 °C for 48 h. The mixture was cooled, concentrated and purified by flash column chromatography on neutral alumina, eluting with dichloromethane/methanol (20:1 to 1:1) to afford the product as a white solid. MS (+CI)  $m/z$  347 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) 8.99 (1H, s), 8.34 (1H, d), 7.97 (2H, d), 7.60 (2H, d), 7.01 (1H, d), 3.3-4.0 (4H, m), 1.8-2.2 (4H, m).

Example 12Ethyl 4'-aminospiro[piperidine-4,2'-[1'H]-(pyrido[2,3-d]pyrimidine)]-1-carboxylate hydrochloride(a) Ethyl 3',4'-dihydro-4'-oxospiro[piperidine-4,2'-[1'H]-(pyrido[2,3-d]pyrimidine)]-1-carboxylate

3-Amido-2-aminopyridine (0.5 g, 3.6 mmol), N-carbethoxy-4-piperidone (0.7 g, 4.02 mmol) and 3A molecular sieves (4 g) in 1M hydrogen chloride in ether (3 ml) and ethanol (10 ml) were heated at reflux for 1 h. The mixture was absorbed onto silica gel and purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (20:1 to 5:1) to afford the product as a white solid (0.8 g). MS (+CI)  $m/z$  291 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) 8.56 (1H, s), 8.36 (1H, s), 8.21 (1H, d), 8.02 (1H, d), 6.80 (1H, dd), 4.04 (2H, q), 3.4-3.62 (4H, m), 1.65-1.92 (4H, m), 1.18 (3H, t).

(b) Ethyl 3',4'-dihydro-4'-thioxospiro[piperidine-4,2'-[1'H]-(pyrido[2,3-d]pyrimidine)]-1-carboxylate

A solution of ethyl 3',4'-dihydro-4'-oxospiro[piperidine-4,2'-[1'H]-(pyrido[2,3-d]pyrimidine)]-1-carboxylate (0.74 g, 2.55 mmol) and Lawesson's reagent (0.62 g, 1.5 mmol) in dioxane (15 ml) was heated at reflux for 2 h. The mixture was absorbed onto silica gel and purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (50:1) to afford the product as a white solid (0.7 g). MS (+CI)  $m/z$  307 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) 10.37 (1H, dd), 8.34 (1H, dd), 8.24 (1H, dd), 8.10

(H, s), 6.76 (1H, dd), 4.04 (2H, q), 3.6-3.78 (2H, m), 3.3-3.5 (2H, m), 1.75-1.90 (4H, m), 1.21 (3H, t).

(c) Ethyl 4'-aminospiro[piperidine-4,2'-[1'H]-(pyrido-[3,4-d]-pyrimidine)]-1-carboxylate hydrochloride

5 To a solution of ethyl 3',4'-dihydro-4'-thioxospiro[piperidine-4,2'-[1'H]-(pyrido[2,3-d]-pyrimidine)]-1-carboxylate (0.5 g, 1.63 mmol) in acetonitrile (20 ml) at room temperature was added iodomethane (0.1 ml, 1.63 mmol). The solution was stirred for 20 h, evaporated and purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol (10:1) as eluent to afford the thioimide. The thioimide was  
10 dissolved in acetonitrile saturated with ammonia (20 ml) and heated at 150 °C in a bomb for 48 h. The solution was evaporated and the residue was purified by flash column chromatography on neutral alumina, eluting with dichloromethane/methanol (10:1) to afford, after being acidified with 1M hydrogen chloride in ether, the product.

MS (+CI)  $m/z$  290 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) 10.34 (1H, s), 9.40 (1H, s), 8.61 (1H, s),  
15 8.41 (1H, s), 8.40 (1H, dd), 8.26 (1H, dd), 6.89 (1H, dd), 4.05 (2H, q), 3.4-3.7 (4H, m), 1.85-2.01 (4H, m), 1.20 (3H, t).

Example 13

20 4-Amino-2-(2-thienyl)-pyrido[3,2-d]pyrimidine hydrochloride

A solution of 2-amidino-3-aminopyridine hydrochloride (0.10 g, 0.47 mmol) and 2-thiophenealdehyde (60 mg, 0.54 mmol) in ethanol (1 ml) was stirred at 50 °C for 18 h. The mixture was cooled, then concentrated and the residue was purified by flash column chromatography on neutral alumina, eluting with dichloromethane/methanol (20:1 to 10:1)  
25 as eluent to afford the product as a brown/red solid, m.p. 186-187 °C.

Example 14

7'-Amino-1-(6-cyano-3-pyridinecarbonyl)spiro[piperidine-4,5'-(4'H)-(thieno[3,2-d]-pyrimidine)] hydroiodide  
30

This was prepared by the method of Example 4 using 1-(6-cyano-3-pyridinecarbonyl)-4-piperidone ethylene ketal (WO 97/14686). M.p. 260-261 °C (dec.).

### Screens

The pharmacological activity of compounds according to the invention was tested in the following screens.

#### Screen 1

The activity of compounds of formula (I), or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, may be screened for nitric oxide synthetase inhibiting activity by a procedure based on that of Förstermann *et al.*, Eur. J. Pharm., 1992, **225**, 161-165. Nitric oxide synthase converts <sup>3</sup>H-L-arginine into <sup>3</sup>H-L-citrulline which can be separated by cation exchange chromatography and quantified by liquid scintillation counting.

Enzyme is prepared, after induction, from the cultured murine macrophage cell line J774A-1 (obtained from the laboratories of the Imperial Cancer Research Fund). J774A-1 cells are cultured in Dulbeccos Modified Eagles Medium (DMEM) supplemented with 10% foetal bovine serum, 4 mM L-glutamine and antibiotics (100 units/ml penicillin G, 100 mg/ml streptomycin & 0.25 mg/ml amphotericin B). Cells are routinely grown in 225 cm<sup>3</sup> flasks containing 35 ml medium kept at 37 °C and in a humidified atmosphere containing 5% CO<sub>2</sub>.

Nitric oxide synthase is produced by cells in response to interferon- $\gamma$  (IFN $\gamma$ ) and lipopolysaccharide (LPS). The medium from confluent culture flasks is removed and replaced with 25 ml (per flask) of fresh medium containing 1 mg/ml LPS and 10 units/ml IFN $\gamma$ . After a period of 17-20 hours in culture, harvesting of cells is accomplished by scraping the cell sheet from the flask surface into the culture medium. Cells are collected by centrifugation (1000 g for 10 minutes) and lysate prepared by adding to the cell pellet a solution containing 50 mM Tris-HCl (pH 7.5 at 20 °C), 10% (v/v) glycerol, 0.1% (v/v) Triton-X-100, 0.1 mM dithiothreitol and a cocktail of protease inhibitors comprising

leupeptin (2 mg/ml), soya bean trypsin inhibitor (10 mg/ml), aprotinin (5 mg/ml) and phenylmethanesulphonyl fluoride (50 mg/ml).

For the assay, 25 µl of substrate cocktail (50 mM Tris-HCl (pH 7.5 at 20 °C), 400 µM NADPH, 20 µM flavin adenine dinucleotide, 20 µM flavin mononucleotide, 4 µM tetrahydrobiopterin, 12 µM L-arginine and 0.025 mCi L-[<sup>3</sup>H] arginine) is added to wells of a 96 well filter plate (0.45µm pore size) containing 25 µl of a solution of test compound in 50 mM Tris-HCl. The reaction is started by adding 50 µl of cell lysate (prepared as above) and after incubation for 1 hour at room temperature is terminated by addition of 50 µl of an aqueous solution of 3 mM nitroarginine and 21 mM EDTA.

Labelled L-citrulline is separated from labelled L-arginine using Dowex AG-50W. 150 µl of a 25% aqueous slurry of Dowex 50W (Na<sup>+</sup> form) is added to the assay after which the whole is filtered into 96 well plates. 75 µl of filtrate is sampled and added to wells of 96 well plates containing solid scintillant. After allowing the samples to dry the L-citrulline is quantified by scintillation counting.

In a typical experiment basal activity is 300 dpm per 75 µl sample which is increased to 1900 dpm in the reagent controls. Compound activity is expressed as IC<sub>50</sub> (the concentration of drug substance which gives 50% enzyme inhibition in the assay) and aminoguanidine, which gives an IC<sub>50</sub> (50% inhibitory concentration) of 10 µM, is tested as a standard to verify the procedure. Compounds are tested at a range of concentrations and from the inhibitions obtained IC<sub>50</sub> values are calculated. Compounds that inhibit the enzyme by at least 25% at 100 µM are classed as being active and are subjected to at least one retest.

In the above screen, the compounds of Examples 1 to 14 were tested and gave IC<sub>50</sub> values of less than 25 µM indicating that they are expected to show useful therapeutic activity.

## Screen 2

Compounds also show activity against the human form of induced nitric oxide synthase as can be demonstrated in the following assay.

Enzyme is prepared, after induction, from the cultured human colon adenocarcinoma cell line DLD1 (obtained from the European Collection of Animal Cell Culture - cell line number 90102540). DLD1 cells are cultured in RPMI 1640 medium supplemented with 10% foetal bovine serum, 4 mM L-glutamine and antibiotics (100 units/ml penicillin G, 100 µg/ml streptomycin and 0.25 µg/ml amphotericin B). Cells are routinely grown in 225 cm<sup>3</sup> flasks containing 35 ml medium kept at 37 °C and in a humidified atmosphere containing 5% CO<sub>2</sub>.

Nitric oxide synthase is produced by cells in response to interferon-γ (IFN-γ) and interleukin-1β (IL-1β). The medium from confluent flasks is removed and replaced with 25 ml (per flask) of fresh medium containing 250 units/ml IL-1β and 1000 units/ml IFN-γ. After a period of 17–20 hours in culture, harvesting of cells is accomplished by scraping the cell monolayer from the flask surface into the culture medium. Cells are collected by centrifugation (1000g for 10 minutes) and lysate prepared by adding to the cell pellet a solution containing 50 mM Tris-HCl (pH 7.5 at 20°C), 10% (v/v) glycerol, 0.1% (v/v) Triton-X100, 0.1 mM dithiothreitol and a cocktail of protease inhibitors including leupeptin (2 µg/ml), soya bean trypsin inhibitor (10 µg/ml), aprotonin (5 µg/ml) and phenylmethylsulphonyl fluoride (50 µg/ml).

For the assay, 25 µl of substrate cocktail (50 mM Tris-HCl (pH 7.5), 400 µM NADPH, 20 µM flavin adenine dinucleotide, 20 µM flavin mononucleotide and 4 µM tetrahydrobiopterin) is added to the wells of a 96-well plate. Test compounds are preincubated with enzyme by adding together with 40 µl of cell lysate (prepared as above) and incubating for 1 hour at 37 °C at the end of which period 10 µl of 30 µM L-arginine and 0.025 µCi of L-[<sup>3</sup>H]-arginine in 50 mM Tris-HCl is added to start the enzymatic reaction. Incubation is continued for a further 1 hour at 37 °C. The reaction is terminated by addition of 50 µl of an aqueous solution of 3 mM nitroarginine and 21 mM EDTA.

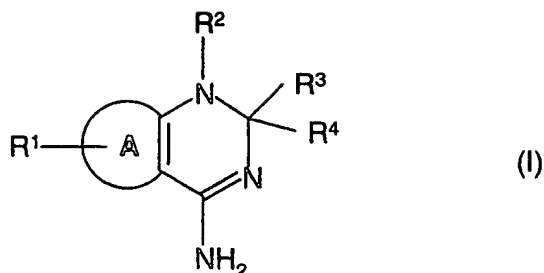
Labelled L-citrulline is separated from labelled L-arginine using Dowex AG-50W. 120  $\mu$ l of a 25% aqueous slurry of Dowex 50W is added to 96 well filter plates (0.45  $\mu$ m pore size). To this is added 120  $\mu$ l of terminated assay mix. 75  $\mu$ l of filtrate is sampled and  
5 added to the wells of 96 well plates containing solid scintillant. After allowing the samples to dry the L-citrulline is quantified by scintillation counting.

In a typical experiment basal activity is 300 dpm per 75  $\mu$ l sample of reagent controls, which is increased to 3000 dpm in the presence of enzyme. Compound activity is expressed  
10 as  $IC_{50}$  (the concentration of drug substance which gives 50% enzyme inhibition in the assay) and L-NMMA, which gives an  $IC_{50}$  of about 0.4  $\mu$ M is tested as a standard to verify the procedure. Compounds are tested at a range of concentrations and from the inhibitions obtained  $IC_{50}$  values are calculated.

15 In this screen the compounds of Examples 1 to 14 give  $IC_{50}$  values less than 25  $\mu$ M, indicating that they are predicted to show useful therapeutic activity.

CLAIMS:

1. A compound of formula (I)



wherein

$R^1$  represents hydrogen, alkyl C1 to 6, alkoxy C1 to 6, halogen or trifluoromethyl;

$R^2$  represents hydrogen or alkyl C1 to 6;

A represents a five membered heterocyclic aromatic ring containing 1 to 3 heteroatoms which

may be the same or different and are selected from O, N and S; or a six membered

heterocyclic aromatic ring containing 1 to 3 nitrogen atoms;

(i)  $R^3$  represents phenyl, a six membered heterocyclic aromatic ring containing 1 to 3 nitrogen atoms, or a five membered heterocyclic aromatic ring containing 1 to 3 heteroatoms which may be the same or different and are selected from O, N and S, which phenyl or

heterocyclic aromatic ring may be optionally substituted by alkyl C1 to 6, alkenyl C2 to 6, alkynyl C2 to 6, alkoxy C1 to 6, halogen, hydroxy, alkylthio C1 to 6, cyano, trifluoromethyl, nitro or a group  $-NR^5R^6$ ;

and  $R^4$ ,  $R^5$  and  $R^6$  independently represent hydrogen or alkyl C1 to 6;

or

(ii)  $R^3$  represents alkyl C1 to 8, alkenyl C2 to 8 or alkynyl C2 to 8;

and  $R^4$  represents hydrogen or alkyl C1 to 6;

or

(iii)  $R^3$  and  $R^4$  together represent  $(CH_2)_a \cdot Z \cdot (CH_2)_b$ , Z representing  $N(COOR^7)$ ,

wherein  $R^7$  represents alkyl C1 to 6 or haloalkyl C1 to 6, or  $R^7$  represents a group

$(CH_2)_n YR^9$  wherein n represents an integer from 2 to 5, Y represents O, S or a bond and



$R^9$  represents alkyl C1 to 6 optionally substituted by halogen or nitro, or  $R^9$  represents phenyl optionally substituted by alkyl C1 to 6, halogen or nitro; and  
a and b independently represent an integer 1 to 3, provided that  $a + b$  is 3 or 4;  
or

- 5 (iv)  $R^3$  and  $R^4$  together represent  $(CH_2)_a \cdot Z \cdot (CH_2)_b$ , Z representing  $N(COR^8)$ ,  
wherein  $R^8$  represents phenyl, a six membered heterocyclic aromatic ring containing 1 to 3  
nitrogen atoms or a five membered heterocyclic aromatic ring containing 1 to 3  
heteroatoms which may be the same or different and are selected from O, N and S, which  
phenyl or heterocyclic aromatic ring may be optionally substituted by alkyl C1 to 6, alkoxy  
10 C1 to 6, halogen, nitro, cyano, trifluoromethyl, alkylsulphonyl C1 to 6 or aminosulphonyl;  
and  
a and b independently represent an integer 1 to 3, provided that  $a + b$  is 3 or 4;  
or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

- 15 2. A compound of formula (I), according to Claim 1, wherein A represents a thieno or  
pyrido ring.

3. A compound of formula (I), according to Claim 2 wherein the compound is a  
thieno[2,3-*d*]pyrimidine or a thieno[3,2-*d*]pyrimidine derivative.

20

4. A compound of formula (I), according to Claim 2, wherein the compound is a  
pyrido[2,3-*d*]pyrimidine, pyrido[3,2-*d*]pyrimidine, pyrido[3,4-*d*]pyrimidine or pyrido[4,3-*d*]  
pyrimidine derivative.

- 25 5. A compound of formula (I), according to any one of Claims 1 to 4 wherein  $R^3$   
represents phenyl, cyclopropyl, ethyl, thiazolyl, ethynyl or furanyl.

6. A compound of formula (I), according to any one of Claims 1 to 5, wherein R<sup>3</sup> and R<sup>4</sup> are in accordance with option (iii) in Claim 1, Z represents N(COOC<sub>2</sub>H<sub>5</sub>), and a and b each has a value of 2.

5 7. A compound of formula (I) which is:

7-amino-4,5-dihydro-5-phenylthieno[3,2-*d*]pyrimidine;

5-cyclopropyl-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine;

5-ethyl-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine;

5-(2-thiazolyl)-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine;

10 5-(2-furyl)-4,5-dihydro-7-aminothieno[3,2-*d*]pyrimidine;

7-amino-4,5-dihydro-5-ethynylthieno[3,2-*d*]pyrimidine;

ethyl 7'-aminospiro[piperidine-4,5'-(4'*H*)-thieno[3,2-*d*]pyrimidine]-1-carboxylate;

ethyl 4'-amino-3'-chlorospiro[piperidine-4,6'-(7'*H*)-thieno[2,3-*d*]pyrimidine]-1-carboxylate;

4'-amino-(4-cyanobenzoyl)-spiro[piperidine-4,2'-(1'*H*)-(pyrido[3,2-*d*]pyrimidine)];

15 4'-amino-(2-thienoyl)-spiro[piperidine-4,2'-(1'*H*)-(pyrido[3,2-*d*]pyrimidine)];

ethyl 4'-aminospiro[piperidine-4,2'-(1'*H*)-(pyrido[3,2-*d*]pyrimidine)]-1-carboxylate;

4'-amino-(4-cyanobenzoyl)-spiro[piperidine-4,2'-(1'*H*)-(pyrido[3,4-*d*]pyrimidine)];

ethyl 4'-aminospiro[piperidine-4,2'-(1'*H*)-(pyrido[3,4-*d*]pyrimidine)]-1-carboxylate;

4'-amino-(4-cyanobenzoyl)-spiro[piperidine-4,2'-(1'*H*)-(pyrido[4,3-*d*]pyrimidine)];

20 ethyl 4'-aminospiro[piperidine-4,2'-(1'*H*)-(pyrido[2,3-*d*]pyrimidine)]-1-carboxylate;

4-amino-2-(2-thienyl)-pyrido[3,2-*d*]pyrimidine;

7'-amino-1-(6-cyano-3-pyridinecarbonyl)spiro[piperidine-4,5'-(4'*H*)-(thieno[3,2-*d*]-pyrimidine)];

or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

25

8. A compound of formula (I) according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, for use as a medicament.

9. A pharmaceutical composition comprising a compound of formula (I) according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.
- 5 10. The use of a compound of formula (I) according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.
- 10 11. The use as claimed in Claim 10 wherein it is predominantly inducible nitric oxide synthase that is inhibited.
12. The use of a compound of formula (I) as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a  
15 medicament, for the treatment or prophylaxis of inflammatory diseases.
13. The use as claimed in Claim 12 wherein the disease is asthma or rheumatoid arthritis.
14. The use of a compound of formula (I) as defined in any one of Claims 1 to 7, or a  
20 pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of pain.
15. The use of a compound of formula (I) as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in combination with a  
25 COX-2 inhibitor, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.
16. A method of treating, or reducing the risk of, human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering a  
30 therapeutically effective amount of a compound of formula (I), as defined in any one of

Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, to a person suffering from, or at increased risk of, such diseases or conditions.

17. A method of treatment according to Claim 16 in which it is predominantly inducible  
5 nitric oxide synthase that is inhibited.

18. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of  
10 Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

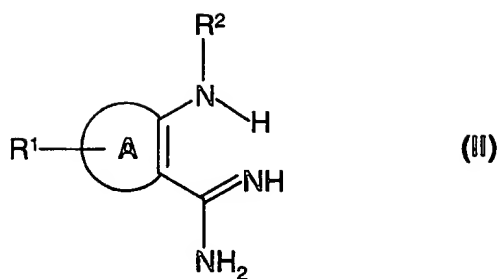
19. The method of treatment as claimed in Claim 18 wherein the disease is asthma or rheumatoid arthritis.

15 20. A method of treating, or reducing the risk of, pain in a person suffering from, or at risk of, said condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

20 21. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a combination of a compound of formula (I), as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, with a COX-2 inhibitor.

25 22. A process for the preparation of the compound of formula (I), as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein the process comprises:

(a) reaction of a compound of formula (II)



wherein A, R<sup>1</sup> and R<sup>2</sup> are as defined above,

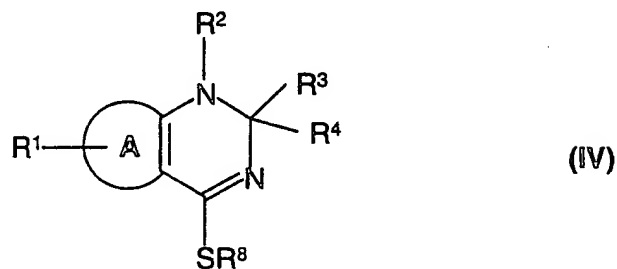
with a compound of formula (III) or an acetal derivative thereof

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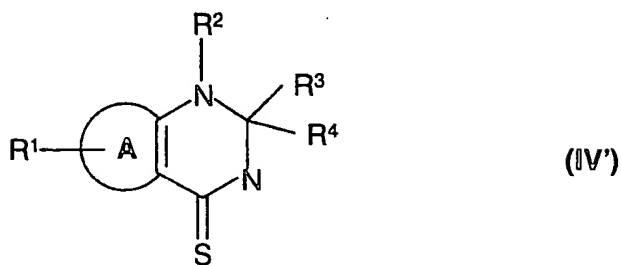


wherein R<sup>3</sup> and R<sup>4</sup> are as defined above; or

(b) reaction of a compound of formula (IV) or (IV')



10



wherein A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined above, and R<sup>8</sup> represents an alkyl group;

with ammonia or an equivalent thereof; or

15

(c) preparation of a compound of formula (I) in which R<sup>3</sup> and R<sup>4</sup> are according to option (i)

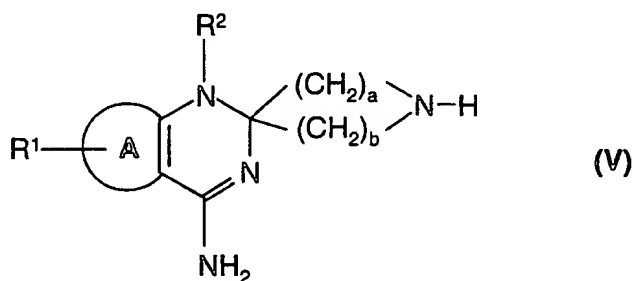
in the general definition of formula (I) given above and one or both of R<sup>5</sup> and R<sup>6</sup> represents

alkyl C1 to 6, by alkylation of a corresponding compound in which one or both of  $R^5$  or  $R^6$  represents hydrogen; or

(d) preparation of a compound of formula (I) in which  $R^2$  represents alkyl C1 to 6, by alkylation of a corresponding compound in which  $R^2$  represents hydrogen; or

5 (e) deprotection of a compound of formula (I) in which one or more nitrogen atoms and/or another atom is protected; or

(f) preparation of a compound of formula (I) in which  $R^3$  and  $R^4$  are in accordance with option (iv) in the general definition of formula (I) given above, by reacting a compound of formula (V)



10 wherein A,  $R^1$ ,  $R^2$ , a and b are as defined above,

with a compound of formula (VI)



15 wherein X represents  $COOR^7$  or  $COR^8$ ,  $R^7$  and  $R^8$  being as above, and L is a leaving group;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof, or vice versa, and

20 where desired converting the resultant compound of formula (I) into an optical isomer thereof.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00641

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 471/04, C07D 471/10, C07D 495/04, C07D 495/10, A61K 31/505  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3403152 A (HERBERT MORTON BLATTER), 24 Sept 1968 (24.09.68)  --	1-15,22
A	US 3483205 A (RICHARD WILLIAM JAMES CARNEY), 9 December 1969 (09.12.69)  -- -----	1-15,22

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

1 July 1998

Date of mailing of the international search report

03-07-1998

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00641

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16-21  
because they relate to subject matter not required to be searched by this Authority, namely:  
A method for treatment of the human or animal body by therapy,  
see rule 39.1.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

09/06/98

International application No.

PCT/SE 98/00641

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3403152 A	24/09/68	NONE	
US 3483205 A	09/12/69	NONE	